

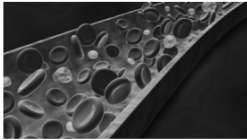
**The Many Faces of Hematologic Disease**  
COPE Course : 54532 - SD

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**Financial disclosure**

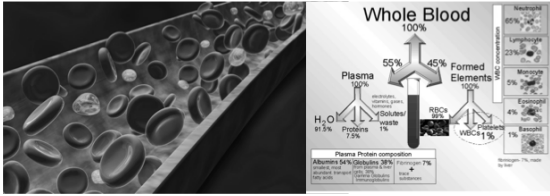
**I have nothing to disclose**

**Hematologic disorders (blood constituents)**



**Blood vessel wall disease (atherosclerosis/diabetes/HT)**

**Rheology**  
The science dealing with the deformation and flow of matter, particularly in a fluid. a science dealing with the deformation and flow of matter; also : the ability to flow or be



**Whole Blood** 100%

- Plasma 55%
  - H<sub>2</sub>O 91.5%
  - Proteins 7.5%
  - Electrolytes 1%
- Formed Elements 45%
  - RBCs 45%
  - WBCs 1%
  - Platelets 4%

**Plasma Protein composition**

- Albumin 54%
- Globulins 28%
  - alpha 1 1%
  - alpha 2 1%
  - beta 1 1%
  - beta 2 1%
  - gamma 1 1%
  - gamma 2 1%
  - gamma 3 1%
  - gamma 4 1%
  - gamma 5 1%
- Fibrinogen 2%
- Other 15%

**Blood flow overview**

Hagen-Poiseuille equation

$$Q = \frac{\Delta P \pi R^4}{8L\eta}$$

Q= blood flow  
ΔP= pressure gradient  
R= radius of blood vessel  
L= length of blood vessel  
η= blood viscosity

**Increase perfusion by:**

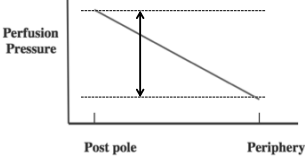
- ↑ numerator (pressure gradient or vessel radius)
- ↓ denominator (decrease viscosity or shorten blood vessels)

**Decreased perfusion from:**

- ↓ numerator (pressure gradient or vessel radius)
- ↑ denominator (increased viscosity or lengthen blood vessels)

**Ocular perfusion pressure concepts**

Perfusion Pressure



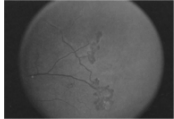
**Post pole**                      **Periphery**

Vitreous gel  
CRA  
CRV  
Macula  
Fovea

Hagen-Poiseuille equation

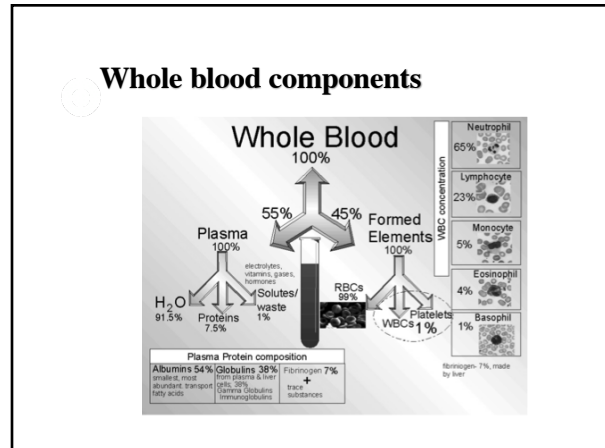
$$Q = \frac{\Delta P \pi R^4}{8L\eta}$$

Q= blood flow  
ΔP= pressure gradient  
R= radius of blood vessel  
L= length of blood vessel  
η= blood viscosity



Variable components for perfusion include:

IOP  
BP  
perfusion gradient  
radius of blood vessel  
blood viscosity /blood components



### Complete Blood Count (CBC)

TEST	RESULT	UNITS	REF RANGE
WBC	5.2	x 1000/mm <sup>3</sup>	3.9 - 11.1
RBC	3.81	x 10 <sup>6</sup> /mm <sup>3</sup>	4.20 - 5.70
HGB	14.5	g/dL	13.2 - 16.9
HCT	41.2	%	38.5 - 49.0
MCV	98	fL	80 - 97
MCH	33.7	pg	27.0 - 33.5
MCHC	35.3	%	32.0 - 36.0
RDW	11.8	%	11.0 - 15.0
PLT	172	x 1000/mm <sup>3</sup>	140 - 390
MPV	7.6	fL	7.5 - 11.5
NEUT %	40.1	%	38.0 - 80.0
LYMPH %	48.1	%	15.0 - 40.0
MONO %	12.9	%	0.0 - 13.0
EOS %	0.6	%	0.0 - 8.0
BAZO %	0.3	%	0.0 - 2.0
NEUT, ABS	2085	cells/mm <sup>3</sup>	1650 - 8000
LYMPH, ABS	2397	cells/mm <sup>3</sup>	1000 - 3500
MONO, ABS	671	cells/mm <sup>3</sup>	40 - 900
EOS, ABS	31	cells/mm <sup>3</sup>	30 - 600
BAZO, ABS	16	cells/mm <sup>3</sup>	0 - 125

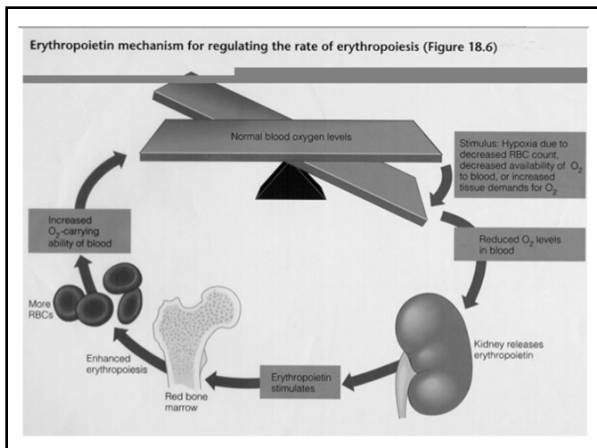
### Red blood cells

Formed in bone marrow

Delivers O<sub>2</sub> to tissues

Deformability needed for capillary circulation

Anemia: ↓ count      Polycythemia: ↑ count



### Case 1: Diabetes and anemia

55 yo WM with sudden vision change in the left eye for a few days. No other changes since last dilated exam 5 mos earlier.

States compliance with Xalatan for OAG OU

Pt treated for DM x 5 years and he thinks the desserts he has been eating caused him to loose vision.

**Medical history**

DM x 5 yrs (A1c 6.7 avg BS 122)  
(Severe NPDR OU 5 mos ago)

Stage 3 colon cancer dx 2 yrs ago  
chemotherapy induced anemia

HTN on meds 124/82

HL on meds with good control

**Clinical findings**

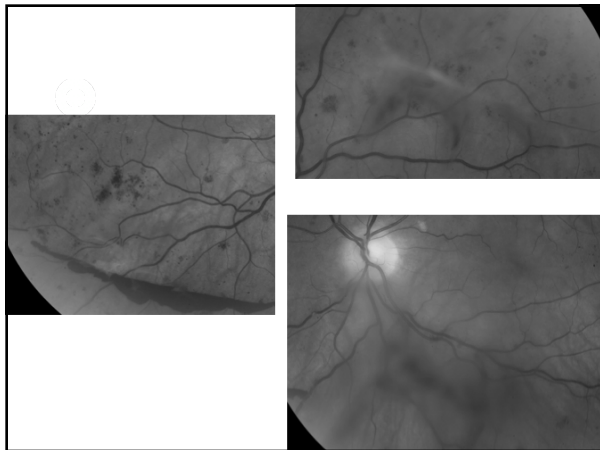
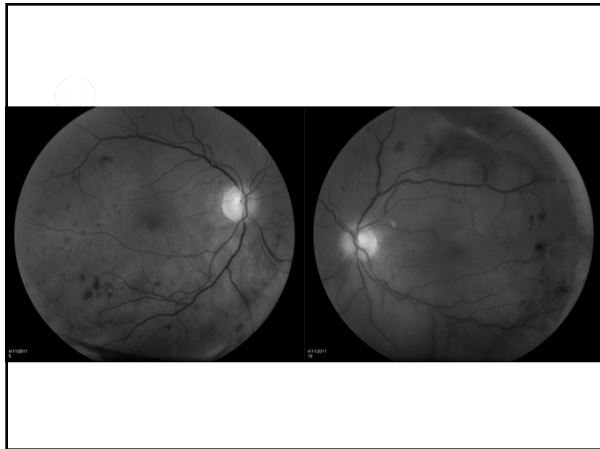
BVA 20/20 OD/OS

P3/4RRL (-) APD

SLE: pinguecula OU  
no NVI OU

Fundus?

TA 11 OD  
14 OS



**This clinical presentation violates the natural course of diabetic retinopathy**

**Progression from severe NPDR to bilateral PDR with vitreous hemorrhage in 5 mos**

### Rates of progression to PDR in diabetic retinopathy

Level of retinopathy	PDR (in 1 year)	HR PDR (in 5 years)
<small>DCCT</small>		
Mild NPDR	5%	15%
<small>ETDRS</small>		
Moderate NPDR	12-27%	33%
Severe NPDR	52%	→ 60-75%
Very severe NPDR	75%	75%

AOA Evidence Based Clinical Practice Guidelines 2014: Eye care of the patient with Diabetes Mellitus

### Lab findings in past year

**DM: A1c 7.3**    **9 mos ago was 6.7**  
**132 average BS past 3 mos**

**Anemia: RBC 3.25-3.51 (4.7-5.43)**  
**HGB 9.6-12.0 (12.3-16.3)**  
**HCT 31.3-33.5 (42-54)**

**\* Severe anemia for Hgb <10 for men**

### Diabetes and anemia

**25% of DM patients are anemic from nephropathy**

**ETDRS: ↓ hemoglobin associated with progression to PDR**

**Reversal/resolution of diabetic retinopathy with treatment of anemia \***

\* Mikajiri K, Nishikawa N: Two cases of diabetes with anemic retinopathy. Association of Ophthalmologica Japonica 2007;Vol 58, 698-702

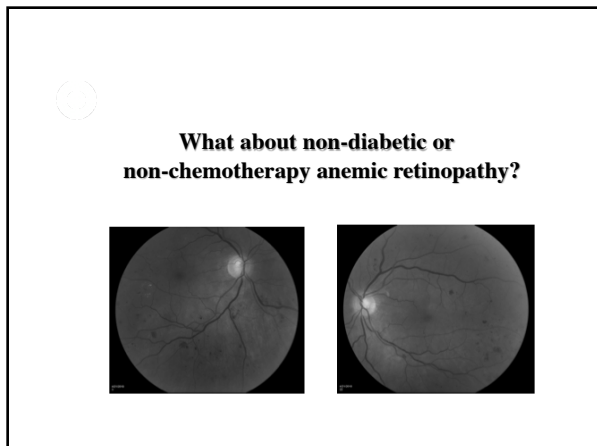
\* Berman DH, Friedman EA. Partial absorption of hard exudates in patients with diabetic end-stage renal disease and severe anemia after treatment with erythropoietin. Retina. 1994;14:1-5.

### Chemotherapy induced NV

Schachat et al.... reported 3 patients with VH heme following chemotherapy for AML.

Wiznia, Rose and Levy reported progressive NVD and NVE in a patient treated for ALL.

Melberg reported case of a pediatric patient with ALL whose diabetic retinopathy progressed from "normal to legal blindness" in 6 months.



Eur J Haematol. 2001 Oct;67(4):238-44.

**Prevalence of retinopathy in patients with anemia or thrombocytopenia.**

Carrara MC<sup>1</sup>, Rossetti L, Gerli GC.

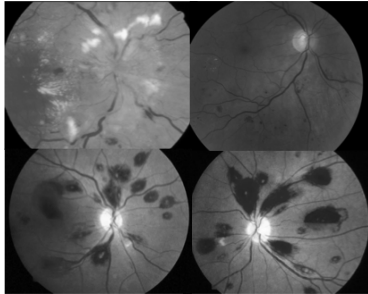
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**Exact mechanism contributing to the clinical picture is unclear unclear**

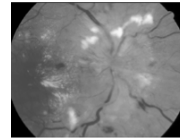
**28.3% incidence of retinopathy present in patients with anemia only**

**38% incidence of retinopathy present in when both anemia and thrombocytopenia are present**

### Shared fundus findings



### Clinical findings in anemic retinopathy



- Superficial and deep retinal hemorrhages
- Cotton wool spots
- Venous tortuosity
- White centered hemorrhages
- Exudates
- Swollen disc/optic neuropathy

### Mechanisms of anemic retinopathy

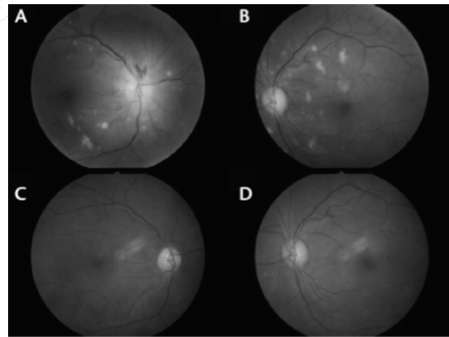
No direct causation identified:

- Anoxia
- venous stasis
- changes in capillary permeability
- arterial angiospasm

Associated contributing factor:

- severity of anemia (ie: Hb <8)
- NOT duration
- increased blood viscosity
- other Myeloproliferative disorders

### Clinical resolution with treatment

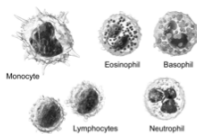


### White blood cells

Formed in bone marrow

Makes up 1% of normal blood volume

Immunologic in function (infection/inflammation)

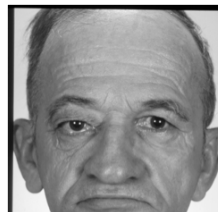


Found in blood and lymphatic vessels

Leukocytosis ↑ in WBC #  
Leukopenia ↓ in WBC #

### Case 2


67 yo WM want new glasses. He has blurry vision OD and sees double looking to right for 2 mos



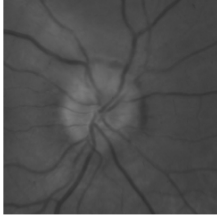
Progressive epiphora OD for past 5 mos

No pain or other symptoms

**BVA 20/30 OD**  
**20/20 OS**  
**P3/4RRL (+) APD OD**  
**SLE: OD: ecchymosis and erythema of upper and lower eyelids with conjunctivochalasis proptosis**  
**OS: dermatochalasis**  
**Hertel: 25 OD x 20 OS**  
**110 base**

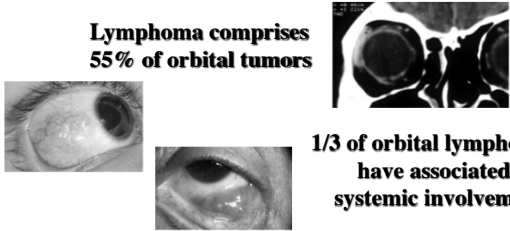


**Clinical findings**  
**Fundus exam:**  
**OD: disc edema**  
**OS: 3/35 sharp margins**  
**No hemorrhage/vascular occlusion**

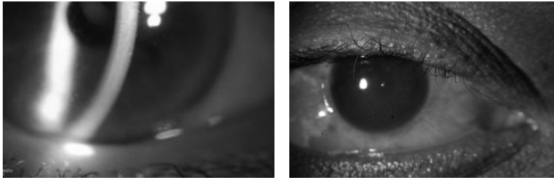


**Clinical findings**  
**MRI: right orbital mass located in the lateral aspect of the mid orbit obscuring detail of the lateral rectus with recommendation for biopsy if clinically indicated**  
**Biopsy proven lymphomatous mass- Non-Hodgkin's lymphoma**

**Lymphoma comprises 55% of orbital tumors**  
**1/3 of orbital lymphomas have associated systemic involvement**  
**Overall survival rate for NHL associated orbital tumors is approximately 60%**



**Non resolving uveitis c/s hypopyon is most common ocular manifestation of lymphoma**



**Pl: Drugs that suppress platelet function [edit]**  
 These drugs are used to prevent thrombus formation.  
**Oral agents [edit]**


- aspirin
- clopidogrel
- cilostazol
- ticlopidine
- ticagrelor
- prasugrel

**Pri**  
**Th: Drugs that stimulate platelet production [edit]**

- thrombopoietin mimetics
- desmopressin
- factor VIIa

**Th**  
**Intravenous agents [edit]**

- abciximab,
- eptifibatid
- tirofiban
- Others oprelvekin, romiplostim, eltrombopag, argatroban

**mation**


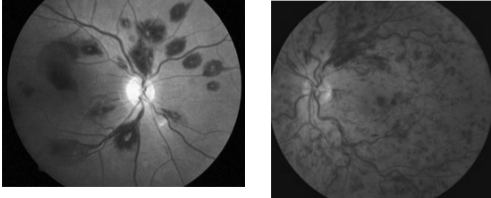
**General indications for CBC**

**Broad screening test to assess health status**  
(ie: anemia, infections, inflammation, bleeding disorders and leukemia)

**Assess/monitor efficacy of treatments**  
(ie: anemia)

**Impact of treatment**  
chemotherapy/radiation

**Hyperviscosity and hypercoagulability syndromes**



**Hyperviscosity syndromes :**

- Lymphoproliferative disorders
  - Lymphomas (ie: non-Hodgkin's)
- Myeloproliferative disorders:
  - Polycythemia vera
  - Leukemias

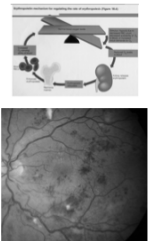
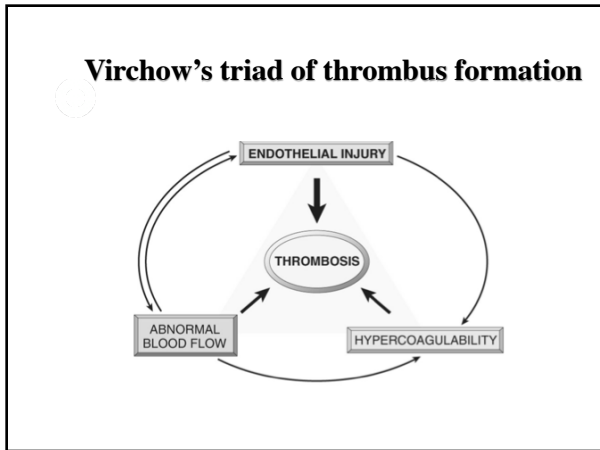
**Hypercoagulability syndromes:**

- Prothrombin Mutations
- Thrombocytosis
- Factor V Leiden
- Antiphospholipid Syndrome
- Homocysteinemia and homocystinuria

**Secondary Polycythemia (Erythrocytosis)**

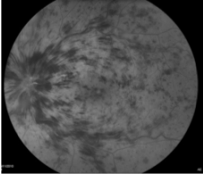
Most commonly related to conditions causing systemic hypoxia:

- COPD/sleep apnea
- heavy smoking
- hypovolemia (ie: severe dehydration)
- congestive heart failure (CHF)
- living/training at high altitude
- long term CO2 exposure
- Ashkenazi Jewish ancestry

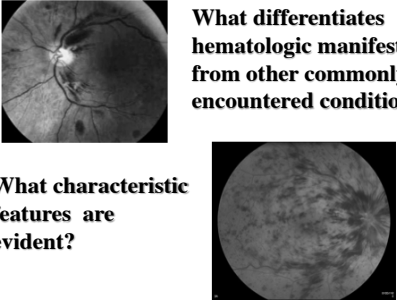
**Common retinal manifestations**

Retinal vein occlusion is the most common ocular manifestation of hyperviscosity and hypercoagulability syndromes



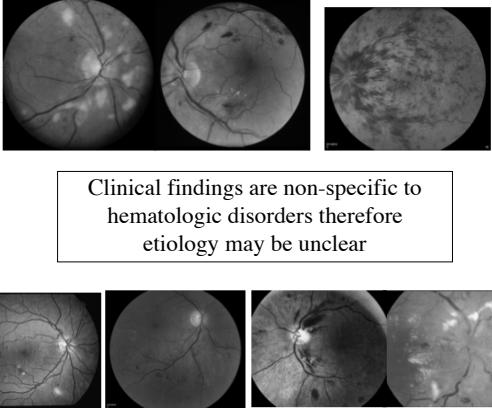
**Incidence in US is**  
**CRVO: .5%**  
**BRVO: 1.8%**

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**What differentiates hematologic manifestations from other commonly encountered conditions?**

**What characteristic features are evident?**



Clinical findings are non-specific to hematologic disorders therefore etiology may be unclear

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**Increased suspicion for underlying hematologic disorders based on clinical appearance**

- **Bilateral/simultaneous presentation**
- **Other thrombotic vascular occlusion**
- **Common diseases deviate from natural course**
- **Familial history of thrombotic processes**

Clinical pathologic reviews

**Seeing through thick and through thin: Retinal manifestations of thrombophilic and hyperviscosity syndromes**

Rithwick Rajagopal, MD, PhD\*, Rajendra S. Apte, MD, PhD\*

Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, Saint Louis, Missouri, USA

**Table 1 – Recommended initial screening tests for atypical retinal vascular occlusion**

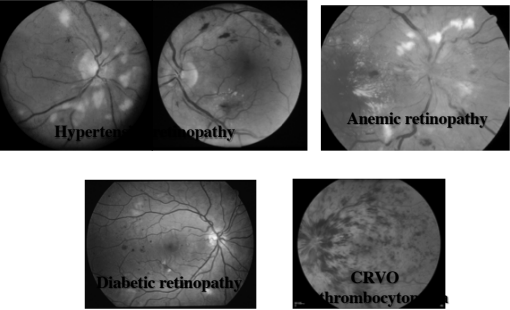
**Hyperviscosity**

- Complete blood count with smear (rouleaux formation may be present in hyperviscosity syndrome)
- Complete metabolic panel
- Protein gap (total protein–albumin): gap >4 may indicate a paraproteinemia
- Direct measurement of serum viscosity (reference range: <1.5 centipoise)

**Hypercoagulability**

- Prothrombin time
- Partial thromboplastin time
- Factor V Leiden assessment
- Prothrombin G20210A mutation screening
- Anticardiolipin antibody screening
- Lupus anticoagulant screening
- Protein C levels
- Protein S levels
- Antithrombin III levels

**Guess the retinopathy**



Hypertensive retinopathy

Anemic retinopathy

Diabetic retinopathy

CRVO thrombocytosis

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**Blood derived products in ocular disease treatment**




**Whole blood**

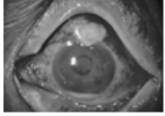
1989- Saprykin et al reported use of whole blood injection following trabeculectomy surgery

proposed theory of effect:


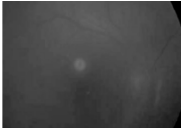
- cellular clogging of outflow
- enhanced fibrin activity



**Whole blood complications**



**Hypohemia**      **Endophthalmitis**      **Vitreous hemorrhage**

**Fibrin**

1909 : initially reported as a tissue adhesive

1940's : Tidrick et al used fibrin for skin graft fixation

1945: Early ophthalmic report by Katzin et al using aqueous fibrin to fix a corneal transplant in a rabbit

**Benefits of fibrin as an adhesive**

Underlying mechanism of action mimics the natural stages of coagulation and adhesion

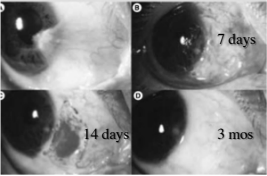
Completely biodegradable in six weeks

No foreign body reaction

Has limited mechanical stretch ability

Requires some prep time

**Fibrin glue for eye surgery**



- Conjunctiva resection
- Strabismus surgery
- Pterygium
- Keratoplasty
- Oculoplastics
- Glaucoma

**Autologous serum eye drops**

Not commercially Available

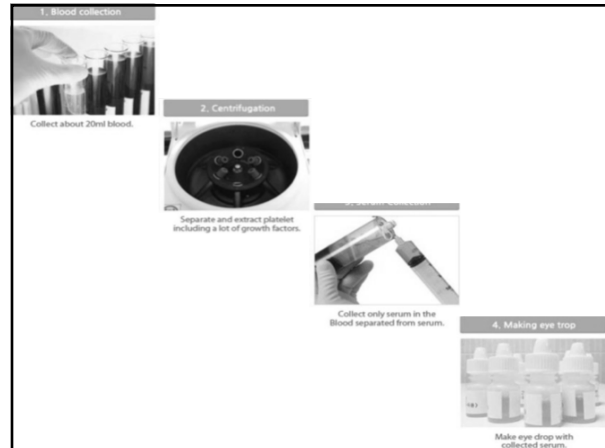
Not routinely covered by insurance

Formulated in compounding pharmacy

- 1. Safety and efficacy of autologous serum eye drops for treatment of dry eyes in graft-versus-host disease. *Amal AA, Karim R, Karim ML, Nishi S, Barney N, Kim K, Longo W, Helmuth P, Juckett M. Ocul Oncol Invest. 2017 Jan;3(2):152-158. doi: 10.1089/oi.2016.0307.152. [Epub 2016 Jul 22]. PMID: 27232993*
- 2. At-Sera Z, Zimmerman A, Bacha RD, Day S, Shah Z, Singh R, Baskin DA. *Cor Pharm Des. 2016;22(2):4470-80. Review. PMID: 27232993*
- 3. Autologous Plasma Rich in Growth Factors Evidences in Refractory Cases of Ocular Surface Disease. *Morayo-Linco J, Sanchez RM, Flores AC, Ariza E, Begoña L, Chue G, Fernandez Vega L. Ophthalmol Res. 2016;5(2):184-1. doi: 10.1155/2016/184. [Epub 2016 Nov 17]. PMID: 28031194*
- 4. Effectiveness of Autologous Serum Eye Drops Combined With Punctal Plugs for the Treatment of Sicca Syndrome-Related Dry Eye. *Lee Y, Hwang JM, Cho K, Cho S, Kwon S, Kawakita T, Tsubota K. Cornea. 2015 Oct;34(10):1214-20. doi: 10.1097/ICO.0000000000000942. PMID: 25925470*
- 5. Long-term use of autologous serum (AS) eye drops for the treatment of dry eye disease. *Hudson M, Shinn RM, Sagar A, Seng H, Woodward SM, Wallace K, Mann D. Cornea. 2014 Dec;33(12):1943-1. doi: 10.1097/ICO.0000000000000271. PMID: 25234923*
- 6. Correlation of clinical efficacies of autologous serum eye drops in patients with primary and secondary Sjögren syndrome. *Heung J, Chung SH, Jeon S, Kwak SH, Park SH, Kim MS. Cornea. 2014 Jul;33(7):963-7. doi: 10.1097/ICO.0000000000000167. PMID: 24582687*

① **Serum constituents**

**Epitheliotropic components:**  
**Epidermal growth factor (EGF)**  
**Transforming growth factor (TGF)**  
**Vitamin A**  
**Substance P**  
**Insulin like growth factor**  
**Cytokines**  
**Fibronectin**



1. Blood collection  
Collect about 20ml blood.

2. Centrifugation  
Separate and extract platelet including a lot of growth factors.

3. Serum collection  
Collect only serum in the blood separated from serum.


4. Making eye drop  
Make eye drop with collected serum.

② **Considerations for serum eye drops**

**Storage:**  
**Temperature:**  
- 4 F unopened and 39.2 F opened  
**Shelf life uncertain**

**Possible organism growth:**  
**Bacterial/fungal growth**  
**Viral infection (HIV and hepatitis)**

③ **Indications for serum drops**



**Dry eye (20/50/100%)**  
**Chronic graft vs host disease**  
**Recurrent erosions**  
**Neurotrophic ulcerations**  
**Bleb leak**  
**Thermal/chemical burn**  
**Stevens- Johnsons disease**

④

**Thank you!**

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